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Pregabalin and intravenous lidocaine for management of postoperative pain and surgical stress response in elective laparotomies: A double blind randomised controlled trial

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Abstract

Introduction: Postoperative pain remains a significant problem in patients undergoing abdominal surgeries, and has a profound effect on patient recovery. High-dose opioids hamper bowel motility and increase nausea and vomiting. Intravenous lidocaine has been used as part of a multimodal analgesia protocol for providing effective pain relief and attenuating surgery-associated inflammatory response. Preoperative pregabalin also has a beneficial effect in reducing pain. This study was carried out to assess the efficacy of combining these drugs in reducing pain, paralytic ileus, and stress response.

Method: Patients undergoing elective laparotomy were randomized into two groups. Group A patients received preoperative placebo and intraoperative lidocaine infusion. Group B patients received preoperative pregabalin and lidocaine. The pain was assessed using a visual analog scale at 2, 6, 18, and 24 hours postoperatively. Morphine consumption on a patient-controlled analgesia pump was also noted. Surgical stress response was assessed by measuring perioperative total leucocyte count, interleukin-6, and C-reactive protein.

Result: Postoperative pain scores at 6, 18, and 24 hours were significantly lower in Group B patients who had received pregabalin. These patients also had lower morphine consumption and earlier bowel recovery as measured by the first passage of stools. Perioperative inflammatory markers were similar in both groups.

Conclusion: Preoperative pregabalin when used with intravenous lidocaine has a synergistic effect on reducing postoperative pain and opioid consumption. This also has a beneficial effect on the return of bowel function.

Keywords: Laparotomy, postoperative pain, surgical stress response, pregabalin, lidocaine

Introduction

Postoperative pain is a major problem following surgery and can increase morbidity. Studies have shown that 86% of patients have moderate to extreme pain following surgery.[1] Its inadequate management can have profound implications on postoperative recovery. Many drugs have been used in the management of pain. Generally, a combination of opioid analgesics and other anti-inflammatory drugs is used. A high dose of opioids, however, increases nausea and vomiting. Abdominal surgeries are associated with significant activation of surgical-stress response with an increase in cytokine and interleukin production further increasing pain perception and ileus.

Ideal postoperative pain management provides adequate pain relief and decreases surgical-stress response with minimum opioid-related side effects.[2] A combination of multiple classes of drugs, "multimodal analgesia", is used to achieve the synergistic effect and has particularly gained popularity for major abdominal surgeries.

Intravenous lidocaine infusion is used as part of multimodal analgesia protocol perioperatively for effective pain relief. It attenuates stress response via anti-inflammatory action.[3] Pregabalin is a gamma-aminobutyric-acid analog primarily used for neuropathic pain. It reduces the hyper-excitability of dorsal-horn sensory neurons induced by tissue injury. Reduction in central sensitization reduces acute and chronic postoperative pain.[4,5] It is believed that lidocaine and pregabalin used together have a synergistic effect in reducing pain and opioid consumption by acting via different mechanisms.[6] Lidocaine acts on the inflammatory component of the surgical-stress response, while pregabalin has a beneficial effect on the neurohumoral response. We performed this study to assess the benefit of adding pregabalin to perioperative lidocaine in reducing pain, postoperative ileus, and stress response in elective laparotomies.

Method

We carried out a prospective, parallel-arm, double-blind, randomized controlled trial. It was carried out in patients undergoing elective open abdominal surgeries in the Department of Surgery at JIPMER, Pondicherry during the period from June 2016 to January 2018. Approval for the study was obtained from the Institute Postgraduate Research Monitoring Committee and the Institute Ethics Committee (Human studies). All authors had access to the study data and reviewed and approved the final manuscript.

Patients above 18 years of age, both male and female, undergoing elective open abdominal surgeries, and belonging to ASA I, II, and III were included in the study. The exclusion criteria included patients sensitive to lidocaine, those suffering from cardiovascular disease or who had preoperative changes on ECG or Echocardiogram, patients on beta-blocker or opioid drugs for other indications, patients receiving perioperative pain relief through an epidural catheter, and patients with functional bowel disorders

Allocation concealment and randomization were ensured by serially numbered opaque sealed envelopes (SNOSE).[7] Envelopes were opened on the day before surgery, and patients were administered either oral pregabalin or a placebo. Lidocaine solution was prepared based on the patient's body weight using 2% lidocaine for intravenous administration (Xylocard; AstraZeneca, Cambridge, UK) and administered as an infusion during surgery. The patients and investigators assessing the outcome postoperatively were blinded. At the end of the study, the envelopes were opened, groups were decoded, and analysis was done. All patients undergoing elective laparotomy during the study period, and meeting the selection criteria were included in the study. Written informed consent was obtained from all patients. The pain was quantified using a visual analog scale, and the operation of patient-controlled analgesia (PCA) pump was demonstrated to the patients preoperatively.

Patients in the control group (*Group A*) received a preoperative placebo and 2% intravenous lidocaine as a bolus dose of 1.5 mg/kg body weight at the time of intubation followed by a continuous infusion at 1.5 mg/kg/h in the intraoperative period and continued up to 1 h post-surgery. Patients in the intervention group (*Group B*) in addition received 150 mg oral pregabalin 12 h before surgery (the night before surgery) and 150 mg on the morning of surgery, followed by the same dose of intravenous lidocaine infusion intra-operatively.

Population characteristics such as age, body weight, and gender were noted. The type of laparotomy performed and the duration of surgery was recorded. Standard anesthesia and analgesia protocol were used in all patients. Perioperative mean blood pressure and heart rate were recorded at 30 min intervals. Intraoperative cardiac monitoring was done to note any manifestations of lidocaine toxicity. Laparotomies were performed by upper or lower midline, or subcostal incisions, depending on the preoperative diagnosis. The drug infusion was continued throughout surgery and up to 1 h postoperatively.

Postoperative pain relief was provided through patient-controlled analgesia (PCA) pump delivering intravenous morphine bolus doses of 1 mg per demand. A lockout period of 15 min was set to avoid overdosage, and the maximum dose was set at 4 mg of morphine over a 4-h period. The pain was assessed in the immediate postoperative period at 2, 6, 18, and 24 h using a visual analog scale (VAS) from 0 to 10. The period to the first analgesic requirement through PCA pump, the number of PCA demands in 24 h, and the total dose of morphine consumed in the first 24 h post-surgery was calculated and noted.

Postoperatively the time to first passage of stools and flatus was noted. Incidence of postoperative nausea and vomiting (PONV) was recorded using a 3-point scale (0 = none, 1 = nausea without vomiting, 2 = vomiting) during the first 24 h after surgery.

Total leucocyte count (TLC) and inflammatory mediators like high sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) were tested in the preoperative period, immediately post-surgery, and 24 hours post-surgery. Serum CRP levels were measured in all patients using high sensitivity CRP (hs-CRP) kits (Calbiotech, CA, USA) containing 96 wells each. This was a sandwich-type ELISA assay. Interleukin-6 levels were measured in all patients using IL-6 ELISA kits (Diaclone, France) containing 96 wells each. Data analysis was done using IBM PASW statistics (SPSS) software version 19.0 (Chicago, IL, USA).

Result

A total of 70 patients undergoing elective open abdominal surgery during the study period were found to satisfy the inclusion and exclusion criteria and gave consent for participation in the study. Of these, 17 were not operated on the designated day of surgery, due to lack of operation theatre time. Hence, 53 patients were included as part of the study. Randomization was done into two groups – Group A or the control group had 27 patients (50.9%), and group B or the intervention group had 26 patients (49.1%). Both groups were similar in age, gender, and body weight distribution (p=0.206 for gender; p=0.066 for age; p=0.375 for bodyweight) Table 1.

The duration of surgery had a non-normal distribution. The median (with interquartile range) duration of surgery was 3.0 (2.0-3.5) h in Group A (range 1-8 hours), and 3.0 (2.0-5.0) h in Group B (range 1-9 hours). There was no statistically significant difference in the duration of surgery between the groups (p=0.633) depicted in Table 1.

The surgeries performed were grouped based on the type of laparotomy. 41 (77.4%) surgeries were done by a midline laparotomy, 5 (9.4%) were subcostal incisions, 4 (7.5%) were right iliac fossa incisions, and 3 (5.7%) were paramedian incisions. The group-wise distribution of the type of surgeries was similar (p=0.673) Fig. 1.

There was a significant difference in pain, as measured by VAS, among the two groups, at 6, 18, and 24 h Table 3. The difference in VAS scores at 2 hours was not significant Fig. 2. The morphine requirement as measured by the "good demands" on the PCA pump was significantly lower in the study group (mean 12.3 ± 3.1 mg in Group A, 9.4 ± 2.4 mg in Group B; p<0.001) Table 2.

Incidence of postoperative nausea and vomiting was noted at 2, 6, 18, and 24 h after surgery. However, there was no significant difference between both groups Table 4.

The mean time to first passage of flatus postoperatively was 42.9 ± 15.1 h in Group A and 38.3 ± 17.3 h in Group B. This difference was not clinically or statistically significant (p=0.311). The mean time to first passage of stools postoperatively was 81.3 ± 34.4 h in Group A and 63.2 ± 22.7 hours in Group B. This was a statistically significant difference (p=0.028).

The additional effect of oral pregabalin on intravenous lidocaine on stress response during surgery was analyzed by measurement of inflammatory mediators like total leucocyte count, C-reactive protein, and interleukin-6 levels in the preoperative period, immediate postoperative period, and 24 hours after surgery Table 5. There was no statistically significant difference due to the addition of pregabalin in the rise in inflammatory mediators from the pre- to postoperative period.

Adverse events such as arrhythmias and hypotension were observed in some of the patients. Although these could not be directly attributed to the use of intravenous lidocaine or oral pregabalin, the occurrence of such events was noted. In patients who had intraoperative hypotension, other factors such as blood loss and the use of anesthetic agents were also considered. In Group A, 2/27 (7.4%) patients had arrhythmia and 3/27 (11.1%) patients had hypotension. In Group B, 1/26 (3.8%) patients had arrhythmia and 2/26 (7.7%) patients had hypotension. There was no significant difference in the occurrence of adverse events in both groups (p=0.765).

Table 1. Demographic data and operative profile

Parameter	Group A	Group B	p-value
Number (n)	27	26	-
Age (y) (Mean ± SD)	52.4 ± 15.4	45.1 ± 12.5	0.066*
Weight (in kg) Mean ± SD	55.4 ± 9.7	57.8 ± 9.8	0.375*
Male: Female	13:14	17:9	0.206~
Duration of surgery (hours) Median (IQR)	3.0 (2.0-3.5)	3.0 (2.0-5.0)	0.633#

* - Student's t test; ~ - Chi-square test; # - Mann-Whitney U test

Table 2. Postoperative morphine requirement over 24 hours

Parameter	Group A (Mean±SD)	Group B (Mean±SD)	p value
First demand (min)	64.4 ± 27.3	94.0 ± 28.0	<0.001*
Total number of demands (up to 24 h)	23.0 ± 9.4	20.0 ± 8.5	0.245*
Total morphine consumption in 24 hours (mg)	12.3 ± 3.1	9.4 ± 2.4	<0.001*

* - Student's t test; h- hours

Table 3. Postoperative VAS scores

VAS score (0 to 10)	Group A (Median with IQR)	Group B (Median with IQR)	p-value
2 h post-op	4.0 (3.0-5.0)	3.0 (2.0-3.0)	0.196#
6 h post-op	6.0 (6.0-7.0)	4.0 (3.0-4.0)	<0.001#
18 h post-op	5.0 (4.0-6.0)	4.0 (3.0-5.0)	0.002#
24 h post-op	4.0 (3.0-5.0)	3.0 (2.0-4.0)	0.009#

- Mann-Whitney U test; h- hours

Table 4. Incidence of postoperative nausea & vomiting

Time	Group A (N=27)		Group B (N=26)		p value
	Nausea	Vomiting	Nausea	Vomiting	
2 h post-op	2	0	0	0	-
6 h post-op	6	0	0	0	-
18 h post-op	3	2	3	0	0.367~
24 h post-op	1	2	1	0	0.367~

~ - Chi-square test; h- hours

Table 5. Perioperative inflammatory markers

Time	Group A	Group B	p-value
Perioperative total leucocyte count (TLC) (Mean±SD)			
Pre-op (cells/mm^3)	7382 ± 2428	7042 ± 1533	0.543*
Immediate post-op (cells/mm3)	10345 ± 3173	9888 ± 2626	0.570*
24 hours post-op (cells/mm3)	11145 ± 2586	10213 ± 2620	0.199*
Perioperative C-reactive protein (Median with IQR)			
Pre-op (mg/L)	6.3 (4.7-12.6)	4.4 (3.2-10.3)	0.084#
Immediate post-op (mg/L)	10.4 (6.8-12.4)	5.9 (5.1-9.4)	0.078#
24 hours post-op (mg/L)	11.2 (8.3-13.4)	8.1 (6.0-12.2)	0.051#
Perioperative Interleukin-6			
Pre-op (pg/mL)	92.382 (55.966-202.545)	51.861 (28.922-113.720)	0.059#
Immediate post-op (pg/mL)	198.372 (129.549-300.257)	159.159 (74.858-312.147)	0.328#
24 hours post-op (pg/mL)	189.167 (125.380-267.533)	163.405 (82.072-249.012)	0.270#

* - Student's t test; # - Mann-Whitney U test

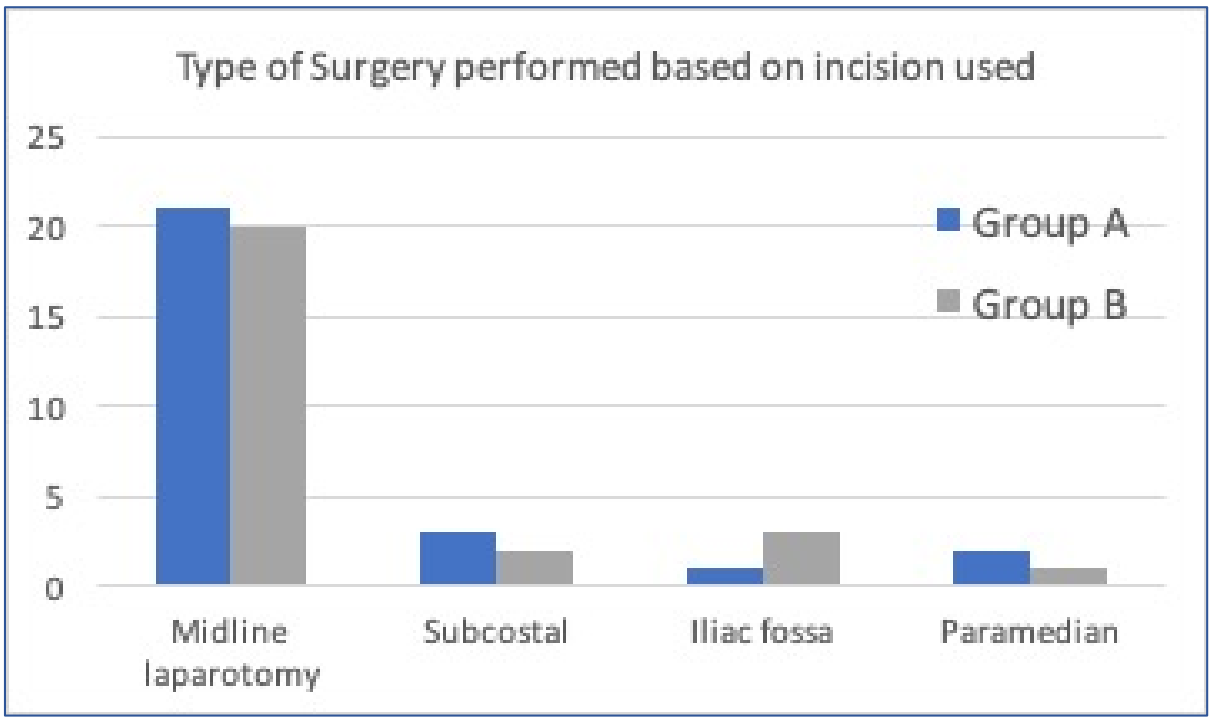

Fig. 1 – Types of surgery performed based on incision

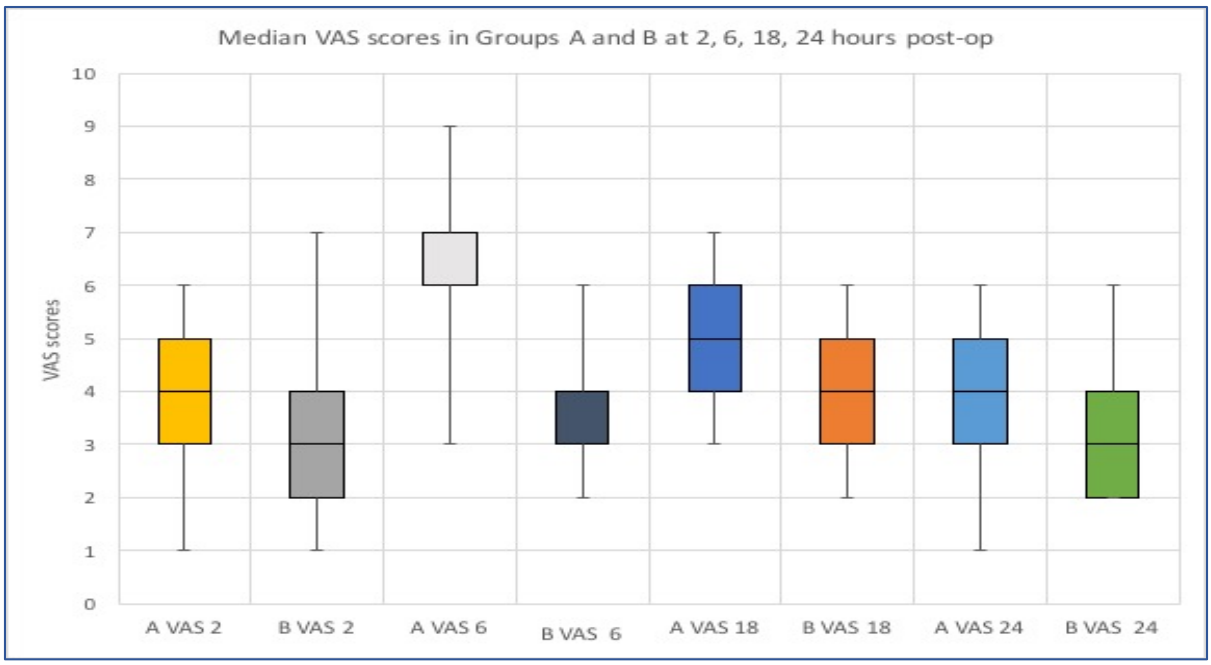

Fig. 2 – Median VAS scores in Groups A and B at 2, 6, 18, 24 hours post-op

Discussion

Postoperative pain continues to remain a major problem due to frequent inadequate pain relief. This is responsible for increased morbidity and has physiological and psychological effects on the patient. Appropriate pain management improves patient satisfaction, reduces the length of hospital stay, and decreases overall health expenditure.

The use of a multimodal analgesia protocol reduces the need for opioid analgesics. This in turn has a significant effect on postoperative bowel recovery and provision of adequate pain relief. Intravenous infusion of lidocaine has been used in abdominal and other surgeries. It is a safe and effective analgesic; it attenuates the surgery-induced inflammatory response and improves gastrointestinal motility.

It has been observed that postoperative pain has a somatic and visceral component, as well as a neuropathic component.[6] Drugs such as gabapentin and pregabalin have been used to control the neuropathic component of postoperative pain.[7] These drugs have been used effectively and safely in the perioperative period.[4, 5] They have also been found to reduce the neurohumoral component of stress response in patients undergoing surgery. Studies have also shown that pregabalin has a beneficial effect on reducing postoperative nausea and vomiting.[9]

In an earlier study by Sridhar P *et al*, perioperative use of lidocaine was compared with placebo (normal saline), and the effect on pain, surgical stress response, and paralytic ileus were studied.[10] It was shown that lidocaine has a significant effect on reducing postoperative pain, stress response, and the incidence of paralytic ileus.[11]

Only one published study was found which compared the use of intravenous lidocaine, preoperative oral pregabalin, and the combination of both.[6] The study considered the effect of combining pregabalin and lidocaine and found that the combination was more effective than either drug alone in reducing the subjective assessment of postoperative pain. Our study was carried out to further corroborate these findings. We sought to study the effect of adding preoperative pregabalin to intravenous lidocaine on reducing pain, the incidence of paralytic ileus, and attenuation of the surgical stress response.

We considered 105 patients undergoing elective laparotomy during the study period. Of these, 70 patients were found to satisfy the study criteria and provided consent. Due to cancellation on the day of surgery, 53 patients were finally included in the analysis – 27 in the control group, and 26 in the intervention group. This sample size was higher than the previous study done which compared the addition of pregabalin and lidocaine, with either drug alone.[3]

In both groups, the type of incision used did not have any influence on postoperative pain. Instead, the duration of surgery and extent of dissection and tissue trauma were likely factors that had a bearing on postoperative pain and analgesic requirement. Patients undergoing surgeries involving the upper gastrointestinal tract had a higher incidence of postoperative nausea and vomiting than patients undergoing other surgeries. Postoperative bowel function recovery was also delayed in patients undergoing major surgeries where the duration of surgery and amount of bowel manipulation were more.

There was a statistically significant difference in VAS scores at 6, 18, and 24 hours ($p<0.05$). This shows that the addition of preoperative oral pregabalin to intravenous lidocaine significantly reduced postoperative pain. As further reinforcement of this finding, patients in Group B also consumed a significantly lower amount of morphine as compared to patients in Group A (9.4 ± 2.4 mg as compared to 12.3 ± 3.1 mg, $p<0.001$).

Nausea and vomiting occurring within 24 hours post-surgery is considered PONV. Inadequate analgesia, heightened stress response, use of emetogenic anesthetic drugs, postoperative ileus, and the administration of high dose opioids, all contribute to the incidence of nausea and vomiting during this period. In our study, none of the patients in Group B had nausea or vomiting up to 6 hours postoperatively. This may have a clinical significance, but statistical significance could not be commented upon. At the 18 and 24-hour mark, there was a slightly lower incidence of nausea and vomiting in the pregabalin group, which was not significant. This difference could be explained due to lower consumption of morphine and the inflammation attenuating effect of pregabalin among patients in Group B.

We also studied the time to first passage of stools and flatus after surgery. We found that patients in Group B who had received preoperative oral pregabalin, and had an overall reduced consumption of morphine, had earlier return of bowel function as assessed by the first passage of stools.

Abdominal surgeries and laparotomies are associated with changes in metabolic, endocrine, hemodynamic, and immune responses. Excessive activation of inflammatory response is responsible for increased postoperative pain and undesirable side effects such as prolonged ileus, nausea, and vomiting.[12] Broadly, the surgical stress response can be divided into an inflammatory response and a neurohumoral response. The stress and tissue reaction accompanying surgery increase the release of cytokines. Proinflammatory cytokines such as IL-6 and IL-8 are responsible for the alteration of neuronal signal transmission.[13] Circulating levels of cytokines are proportional to the extent of tissue trauma during surgery.[14] Inadequate control of pain increases the amount of cytokines released.[15] These inflammatory mediators, in turn, may prolong and aggravate pain by increasing hyperalgesia.

The earlier study by Sridhar *et al* had considered the effect of intravenous lidocaine on inflammatory markers such as total leucocyte count, interleukin-6, and C-reactive protein.[10] They found that these markers were significantly lower in the immediate postoperative period in the lidocaine group. In our study, we sought to study the additional effect of pregabalin on reducing the surgical stress response. TLC, IL-6, and CRP levels were measured in the preoperative, immediate postoperative, and 24 hours post-op periods. There was no difference in the baseline levels of these

markers among both groups (p=0.543 for TLC, p=0.084 for CRP, p=0.059 for IL-6). Our study found that there was no significant difference in the levels of these markers at either the immediate postoperative stage or at 24 hours after surgery (p>0.05). Hence, we could not find any additional benefit of pregabalin in reducing these inflammatory markers. Pregabalin, as discussed earlier, affects the neurohumoral component of the surgical response. IL-6 and CRP are mainly markers of inflammation, and this is perhaps why no significant difference was noted in the levels of these markers on further addition of pregabalin.

The concept of multimodal analgesia is bound to only grow further in the years to come.[16] As has been shown, intravenous lidocaine and preoperative administration of pregabalin are safe and valuable adjuncts to the armamentarium of surgeons for managing postoperative pain, while simultaneously reducing complications such as paralytic ileus and vomiting. Meta-analyses demonstrated benefits with the use of IV lidocaine as a bolus and infusion regime in the perioperative period including a reduction in analgesic requirements, reduced post-operative ileus, and PONV. There was a 60% reduction in opioid consumption with an overall reduced length of hospital stay. There was also a reduced stress response measured by a reduction in IL-8, IL-6, and C3a activation.[17,18] When combined with pregabalin, the effect is synergistic. These drugs ought to become part of the multimodal pain-management system for abdominal surgeries. The significant reduction in VAS score post abdominal surgeries as reported in systematic review form a convincing basis for the use of IV lidocaine, more so with combined pregabalin.[19,20] Further studies with much larger sample sizes and a wider application of these drugs may be carried out to further espouse their benefit.

Conclusion

Preoperative pregabalin when used with intravenous lidocaine has a synergistic effect on reducing postoperative pain and opioid consumption. This also has a beneficial effect on the return of bowel function.

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Conflict of Interest

We hereby declare that none of the contributing authors had any conflict of interest. The study was carried out using an intramural grant obtained for a research project from the institute. Informed consent was taken from all participants of the study. Institutional Ethics Committee clearance was taken before the commencement of the study.

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Author Contribution

Both the authors read and approved the final manuscript. Both the authors participated in the conceptualization, title selection, and manuscript preparation & review; JR: designing, searching or literature review, data collection & analysis, manuscript preparation & review.

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